Dosimetric advantages of generalised equivalent uniform dose-based optimisation on dose–volume objectives in intensity-modulated radiotherapy planning for bilateral breast cancer

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Objective: We compared and evaluated the differences between two models for treating bilateral breast cancer (BBC): (i) dose–volume-based intensity-modulated radiation treatment (DV plan), and (ii) dose–volume-based intensity-modulated radiotherapy with generalised equivalent uniform dose-based optimisation (DV-gEUD plan).

Methods: The quality and performance of the DV plan and DV-gEUD plan using the Pinnacle³® system (Philips, Fitchburg, WI) were evaluated and compared in 10 patients with stage T2–T4 BBC. The plans were delivered on a Varian 21EX linear accelerator (Varian Medical Systems, Milpitas, CA) equipped with a Millennium 120 leaf multileaf collimator (Varian Medical Systems). The parameters analysed included the conformity index, homogeneity index, tumour control probability of the planning target volume (PTV), the volumes $V_{20\text{ Gy}}$ and $V_{30\text{ Gy}}$ of the organs at risk (OAR, including the heart and lungs), mean dose and the normal tissue complication probability.

Results: Both plans met the requirements for the coverage of PTV with similar conformity and homogeneity indices. However, the DV-gEUD plan had the advantage of dose sparing for OAR: the mean doses of the heart and lungs, lung $V_{20\text{ Gy}}$, and heart $V_{30\text{ Gy}}$ in the DV-gEUD plan were lower than those in the DV plan ($p < 0.05$).

Conclusions: A better result can be obtained by starting with a DV-generated plan and then improving it by adding gEUD-based improvements to reduce the number of iterations and to improve the optimum dose distribution.

Advances to knowledge: The DV-gEUD plan provided superior dosimetric results for treating BBC in terms of PTV coverage and OAR sparing than the DV plan, without sacrificing the homogeneity of dose distribution in the PTV.

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Radiology

Breast cancer is the most common cancer and the leading cause of cancer deaths in females worldwide, with about 500 000 fatalities each year. In the USA and Europe, breast cancer constitutes, on average, one in four cancer cases among females [1, 2]. Breast cancer among females in Asian countries mostly occurs between the ages of 40 and 50 years; however, in females in Western countries, it mostly occurs between the ages of 50 and 60 years [2, 3].

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Bilateral breast cancer (BBC) is very rare, accounting for only 1–3% of all breast cancer cases [4–6]. Generally, no treatment guidelines exist for BBC. The treatment of BBC relies on surgery, chemotherapy and radiation therapy; additionally, BBC has previously demonstrated a poor prognosis. Current evidence indicates that the survival rate of patients with BBC is similar to that of patients with unilateral breast cancer [7, 8]. The difficulty in treatment planning for BBC varies greatly, case by case, and is thus a great challenge for radiotherapy. Important issues have been raised concerning how to reduce the dose of radiation to normal tissues, how to maintain a certain tumour control probability (TCP) and how to improve the quality of life for patients with BBC.

Most intensity-modulated radiotherapy (IMRT) planning systems apply dose–volume (DV)-based objective functions for dose optimisation, and an acceptable plan can be generated in most cases. For more complex plans,

more iterations are required because many parameters need to be finely tuned. A successful improvement tool—the generalised equivalent uniform dose (gEUD)—was developed with fewer parameter settings [9–13] to improve the quality of plans. However, gEUD-based optimisation cannot demonstrate such advantages on the first run; more iterations are required to sculpt the dose distribution [14].

To overcome the disadvantages mentioned above, we started with a DV-generated plan, and then improved it by adding gEUD-based improvements. The goal was to reduce the number of iterations and to improve the optimum dose distribution. This method first determined the approximate solutions for most of the treatment targets by DV-based optimisation, and then adjusted the DV histogram (DVH) by gEUD-based optimisation to obtain a superior solution. This study also compared and evaluated the differences between two different methods for the treatment of BBC—(i) a DV plan with DV-based optimisation (DV plan), and (ii) a DV-gEUD plan with mainly DV-based optimisation assisted by gEUD-based optimisation (DV-gEUD plan)—thus providing a quantitative indicator model for reference.

Methods and materials

Research samples and contouring

All 10 patients were immobilised using a tailor-made thermoplastic cast in the supine position with their arms placed above the head holding a T-shaped holder. The patients were scanned using X-ray CT (LightSpeed RT¹⁶; GE Medical System, Waukesha, WI) with a 5 mm slice thickness, containing 512 × 512 pixels per slice. The treatment fields were technically unresectable or medically inoperable in 7 of 10 patients. This cannot be accomplished well using the “tangential fields” technique; therefore, we conducted the present study.

With breast radiation treatment, breast tissue with or without locoregional lymph nodes is considered to be the clinical target volume (CTV). The planning target volume (PTV) was delineated by the oncologist using CT images with the clinically placed wires. To avoid interobserver variations in contouring, the same oncologist outlined all cases. Glandular tissue was visualised by CT with the following boundaries: anteriorly, 0.5 cm under the skin; posteriorly, the PTV was typically bound by the anterior aspect of the ribs and chest wall muscles; medially, 0.5–1 cm to the middle axillary line (not possible for a medial tumour); and laterally, the visualised breast was used to assist the contouring (excluding the axillary tail). In general, a 0.5 cm margin was added to each CTV to give a PTV based on departmental calculations of systematic and random errors. The PTV remained 0.3 cm away from the skin’s surface to ensure some skin sparing. No absolute dose constraints existed for the organs at risk (OAR) (e.g. the heart and lungs). Healthy tissue was evaluated to better control hot spots within the patient volume. Healthy tissue was defined as the difference between the patient’s entire body and all other OAR and the 1 cm expansion of the PTV. The characteristics of the patients are presented in Table 1. This study was approved by our hospital’s institutional review board (IRB 99-2173B and IRB 99-1420B).

Table 1. Patient characteristics (n=10)

Characteristics	Value
Age, median years (range)	47 (27–67)
Stage ^a	T2–T4
Prescribed dose (Gy)/fractions	50.4/28
Structure (cm ³)	
PTV	1962.0 ± 1013.1 (720–3408)
Heart	450.7 ± 107.0 (238–555)
Total lung	2444.9 ± 247.5 (2108–2762)

PTV, planning target volume.

Data are reported as mean ± 1 standard deviation computed over the cohort of 10 patients.

^aAmerican Joint Committee on Cancer version 6.

Treatment planning (DV plans and DV-gEUD plans)

Treatment planning was performed using the Pinnacle^{3®} treatment planning system (TPS) (version 8.0 m; Philips, Fitchburg, WI) with direct machine parameter optimisation (DMPO); the DV plans and DV-gEUD plans were regenerated, respectively, for comparison. All plans were created using the same 6 MV photon beams commissioned for a Varian 21EX linear accelerator (Varian Medical Systems, Milpitas, CA) equipped with a Millennium 120 leaf multileaf collimator (Varian Medical Systems) with a leaf width of 5 mm at the isocentre for the central 20 cm, and 10 mm in the outer 2 × 10 cm, with a maximum leaf speed of 2.5 cm s⁻¹ and leaf transmission of 1.8%. The dose prescribed for the PTV was 50.4 Gy per 28 fractions. The IMRT plans were configured with 12 fixed gantry angles in the International Electronic Commissioning scale along both sides of the breasts [15] at 120°, 100°, 80°, 340°, 320° and 300° for the left breast, and 60°, 40°, 20°, 280°, 260° and 240° for the right breast. The reasons for the selection of these beams were as follows: (i) to limit the number of beams for a single side of a breast to between approximately five and seven, as recommended by Fogliata et al [16]; (ii) to protect the lungs and heart while avoiding angles from the posterior of the patient; and (iii) to achieve directions similar to that in the tangential field treatment method.

The main objective of the treatment plan was to ensure that 95% of the prescribed doses covered 95% of the PTV, and to restrict the dose for OAR as much as reasonably possible; the details of the absolute tolerance levels will be described shortly. The overall workflow is shown in Figure 1. The treatment steps were as follows.

- Step 1 Run the DV-based optimisation to generate a DV plan with respect to the DV criteria.
- Step 2 When the criteria were not satisfactory (see the parameters listed in section DV-based IMRT plan), the following steps were taken:
 - Run DV-based optimisation again to optimise the fluence maps of the treatment plan generated in Step 1.
 - Set the gEUD constraints on the original DV plan based on the DVHs, and then adjust and further optimise the fluence maps (the details of the objectives and constraints can be found in Table 2).
- Step 3: If the treatment plan was acceptable, optimisation was stopped; if it was unacceptable, Step 2 was repeated.

Figure 1. Experimental flowchart. gEUD, generalised equivalent uniform dose; TPS, treatment planning system.

DV-based IMRT plan (DV plan)

The DV plan was designed with a standard 12 field coplanar arrangement and optimised with the DMPO module. The prescribed dose/fractionation of the PTV was set at 50.4 Gy per 28 fractions, $V_{95\%} > 95\%$. The DV constraints were as follows: heart, $D_{\max} < 30$ Gy; total lung, $V_{20\text{ Gy}} < 20\%$; and healthy tissue $D_{\max} \leq 44$ Gy. DV optimisation was run repeatedly until the results were acceptable to the oncologist. The resolution of the dose calculation grid and the bin size were $0.4 \times 0.4 \times 0.4$ cm and 0.01 Gy, respectively, thus ensuring that they were unbiased for the subsequent computation of various indices. The contouring of the PTV and OAR and

confirmation of the results of the treatment plan evaluation were performed by the same oncologist, while the treatment plan was carried out by the same physicist.

DV-based intensity-modulated radiotherapy with generalised equivalent uniform dose-based optimisation (DV-gEUD plan)

The ordinary plan was added to a gEUD objective to assist the optimisation process [11], and the beam angles and DV objective (DVO) settings were the same as those in the DV plan above. Three gEUD objective options can generally be selected in the Pinnacle³ TPS: Target EUD and Min EUD can be selected for the PTV, while Max EUD is used for OAR. This study set the PTV target as follows: EUD, 51 Gy; heart maximum EUD, 25 Gy; and total lung maximum EUD, 10 Gy.

Dose evaluation parameters

The DV plan and DV-gEUD plan were compared as follows: for the PTV, the conformity index (CI), homogeneity index (HI) [17–19], and TCP were used; for the OAR, the mean dose, DV indicator, normal tissue complication rate (NTCP), $V_{30\text{ Gy}}$ and $V_{20\text{ Gy}}$ were used. They are described in detail below.

Conformity index

The CI is used to evaluate the conformal coverage of the PTV by the isodose volume prescribed in the treatment plan [17]. $CI = V_{PTV} \times V_{TV} / TV_{PV}^2$ (V_{TV} , volume of actual prescribed dose; V_{PTV} , volume of PTV; TV_{PV} , volume of V_{PTV} within V_{TV}); at $CI = 1$, optimal treatment conformity is achieved.

Homogeneity index

Homogeneity of the PTV is the aim of the treatment plan. $HI = D_{5\%} / D_{95\%}$ ($D_{5\%}$ and $D_{95\%}$ are the minimum doses delivered to 5% and 95% of the PTV, respectively). The larger the HI value, the lower the homogeneity.

EUD [9, 10, 14, 20]

The basic idea behind the EUD is to identify the uniform dose that provides the same biological effect for

Table 2. Planning objectives and constraints

Organ	DV plan	DV-gEUD plan
PTV	50.4 Gy (uniform dose) $V_{95\%} > 95\%$	50.4 Gy (uniform dose) $V_{95\%} > 95\%$ Target EUD=51 Gy, $a = -7.2$
Total lung	$V_{20\text{ Gy}} < 20\%$ Mean lung dose < 15 Gy	$V_{20\text{ Gy}} < 20\%$ Mean lung dose < 15 Gy Max EUD=10 Gy, $a = 1$
Heart	$D_{\max} < 30$ Gy	$D_{\max} < 30$ Gy Max EUD=25 Gy, $a = 3$
Healthy tissue	$D_{\max} \leq 44$ Gy	$D_{\max} \leq 44$ Gy

DV plan, dose-volume based intensity-modulated radiotherapy; DV-gEUD plan, dose-volume with generalised equivalent uniform dose based intensity-modulated radiotherapy; NTCP, normal tissue complication probability; PTV, planning target volume; $V_{x\text{ Gy}}$, per cent volume receiving $\geq x$ Gy dose; $V_{z\%}$, volume receiving $\geq z\%$ of the prescribed dose.

a given non-uniform dose distribution. The dose level of that uniform dose is then the EUD of the non-uniform distribution. The concept of EUD (voxel based) was first proposed by Niemierko [9] in 1997. Li et al [21] and Deasy [22] derived the following formula for normal tissue:

$$\text{EUD} = \left(\frac{1}{N} \sum_{i=1}^N d_i^a \right)^{1/a} \quad (1)$$

where d_i is the dose in voxel i , N is the number of voxels in the ROI, and a is the volume parameter.

A more general EUD formula was proposed in 1999 by Niemierko [10]: the power law-based gEUD [12, 23]; the equation is slightly modified to allow voxels to be only partially included in the ROI. The calculated gEUD was based on the DVH data without voxel-wise iteration through the entire dose volume. The time needed to calculate the gEUD can be reduced significantly using this method. With v_i denoting the fraction of the ROI that is occupied by voxel i , the gEUD (DVH-based) [23] has the following simple formula:

$$\text{gEUD} = \left(\sum_{i=1}^N v_i d_i^a \right)^{1/a} \quad (2)$$

As shown in equation 2, for $a=1$, the power law-based gEUD becomes the arithmetic mean dose, normally for parallel organs. When $a<1$, it weighs more on the low-dose area, normally for target volumes; by contrast, when $a>1$, it weighs more on the high-dose area, normally for serial organs.

The EUD formula used in Pinnacle³ TPS is the gEUD (Equation 2) for optimisation processing. The gEUD values used for the PTV, lung and heart were -7.2 , 1 and 3 , respectively [20].

Under a non-uniform dose, the gEUD can be used to reflect the damage to tumours and OAR [24, 25]. The EUD leads to the formulation of an objective function for optimisation. The objective function can be written as follows (for full details, see references [11, 26]):

$$F = \prod_{\text{OAR}} f_{\text{OAR}} \cdot \prod_T f_T, \quad (3)$$

where the component subscore f , which can be either for the tumours (Ts) or the OAR, is:

$$f_{T,\text{OARs}}(\text{EUD}) = \theta(\text{EUD}, \text{EUD}_0) \cdot \left[\frac{\text{EUD} - \text{EUD}_0}{\text{EUD}_0} \right] \quad (4)$$

with $\theta = (\text{EUD}, \text{EUD}_0) = H(\text{EUD} - \text{EUD}_0)$, for EUD_{max} ; $\theta(\text{EUD}, \text{EUD}_0) = 1$, for the target EUD; $\theta(\text{EUD}, \text{EUD}_0) = H(\text{EUD}_0 - \text{EUD})$, for EUD_{min} .

The function $H(\cdot)$ is the Heaviside step function (or unit step function); EUD_0 is the desired dose parameter for target volumes and the maximal tolerable dose for OAR.

TCP/NTCP

The EUD-based TCP/NTCP formula [10, 26] derived by Niemierko was used [10, 20].

$$\text{TCP} = \frac{1}{1 + \left(\frac{\text{TCD}_{50}}{\text{EUD}} \right)^{4/\gamma_{50}}} \quad (5)$$

and

$$\text{NTCP} = \frac{1}{1 + \left(\frac{\text{TD}_{50}}{\text{EUD}} \right)^{4/\gamma_{50}}}, \quad (6)$$

where TCD_{50} is the absorbed dose producing a 50% control rate of the tumour exposed to uniform radiation, γ_{50} is a unitless model parameter for describing the slope of the tumour dose-response curve, and TD_{50} is the tolerance dose producing a 50% complication rate within a specific period of time. The present study calculated the TCP and NTCPs of the heart and lungs under two treatment plans [18, 20].

Dose-volume indicators

- A Observe the dose received by a specific volume of OAR ($D_{0.1 \text{ cm}^3}$, $D_{0.5 \text{ cm}^3}$, $D_{1 \text{ cm}^3}$, $D_{2 \text{ cm}^3}$, $D_{5 \text{ cm}^3}$, $D_{10 \text{ cm}^3}$, $D_{25 \text{ cm}^3}$, and $D_{50 \text{ cm}^3}$), where $D_{0.1 \text{ cm}^3}$ denotes the dose in a 0.1 cc volume of the organ (Gy).
- B Observe the volume of the OAR that receives a specific percentage of the dose ($V_{100\%}$, $V_{90\%}$, $V_{50\%}$, $V_{10\%}$ and $V_{5\%}$), where $V_{90\%}$ denotes the volume percentage of the organ that received 90% of the prescribed dose ($50.4 \text{ Gy} \times 90\% = 45.36 \text{ Gy}$).
- C $V_{30 \text{ Gy}}$ and $V_{20 \text{ Gy}}$. The V_{dose} (i.e. $V_{30 \text{ Gy}}$ and $V_{20 \text{ Gy}}$) parameter is defined as the percentage of the CT-defined heart or total lung volume that received a dose greater than or equal to the threshold dose (30 or 20 Gy; heart $V_{30 \text{ Gy}}$ and lung $V_{20 \text{ Gy}}$, respectively) [27–32].

Generally, for the same volume or dose, the smaller the value of $V_{\text{xx}\%}$ or $V_{\text{xx Gy}}$, the better the quality of the plan.

Statistical analysis

The differences between the DVH parameters of the DV plan and the DV-gEUD plan were analysed using a two-tailed exact paired t -test (each pair in the test consisted of patient-specific DVH values). Statistical significance was set at $p \leq 0.05$. Statistical Package for the Social Sciences (SPSS) software was used for data processing (version 16.0; IBM SPSS, Inc., Chicago, IL).

Results

Planning target volume

The isodose curve distribution of the DV plan and DV-gEUD plan for a typical case is shown in Figure 2a,b;

Figure 2. Isodose distributions on transverse and coronal views for one representative BBC sample planned by the (a) DV plan and the (b) DV-gEUD plan. BBC, bilateral breast cancer; DV plan, dose-volume-based intensity-modulated radiation treatment plan; DV-gEUD plan, dose-volume-based intensity-modulated radiotherapy plan with generalised equivalent uniform dose-based optimisation.

the DVH is presented in Figure 3a. The results of the dose evaluation are presented in Table 3. All 10 plans included in the present study were clinically acceptable. The CI, HI and TCP were similar in the two plans.

Organs at risk

DVHs for the heart, lungs and healthy tissue are presented in Figure 3b–d, while the results of the dose evaluation are presented in Tables 4 and 5.

Heart

In Table 4, the mean dose, $V_{30\text{Gy}}$, and NTCP of the heart in the DV plan were higher than those in the DV-gEUD plan ($p < 0.05$), indicating that the DV-gEUD plan had better dose sparing of the heart. For the heart, the doses for the different volumes, as well as the volume receiving different percentages of the prescribed dose

($D_{2\text{cm}^3}$, $D_{5\text{cm}^3}$, $D_{10\text{cm}^3}$, $D_{25\text{cm}^3}$, $D_{50\text{cm}^3}$ and $V_{50\%}$), showed better performance in the DV-gEUD plan.

Lung

The mean dose, $V_{20\text{Gy}}$, $V_{30\text{Gy}}$ and NTCP of the lung in the DV-gEUD plan were lower than those in the DV plan ($p < 0.05$), indicating that the DV-gEUD plan was better at reducing the dose to the lungs. $D_{25\text{cm}^3}$, $D_{50\text{cm}^3}$, $V_{10\%}$ and $V_{50\%}$ showed better performances in the DV-gEUD plan (Table 5).

Healthy tissue

Table 5 shows that the mean doses received in the two plans were similar, with no statistically significant difference.

Beam-on time, monitor unit used and plan time

The beam-on time and total monitor unit (MU) used were equivalent in the two plans, with no statistically significant differences. Regarding the plan time, the DV-gEUD plan [39.32 ± 9.11 min (28–50 min)] was significantly shorter than the DV plan [58.74 ± 15.40 min (40–80 min)], [mean $\pm$ standard deviation (range)].

Discussion

The difficulty in treatment planning for BBC varies greatly. Because the PTV is large with a wide irradiation field size, the lungs and heart might be exposed to relatively high doses of radiation. Most previous publications have considered the two following aspects: (i) heart status and heart diseases induced by radiotherapy, including (a) acute injuries (e.g. pericarditis) and (b) late effects (e.g. congestive heart failure, ischaemia, coronary artery disease and myocardial infarction) [33, 34]. Previous research has revealed that if the heart dose is $>30\text{Gy}$, the risk of coronary heart disease exists, whereas if the mean heart dose is $<26\text{Gy}$ the risk of pericarditis is significantly reduced [27, 28, 30, 31]. In the present study, the mean heart doses in the two plans were both $<20\text{Gy}$. The $V_{30\text{Gy}}$ of the heart was lower in the DV-gEUD plan than in the DV plan. The mean doses for healthy tissue were identical in the two plans. (ii) Lung status: the $V_{20\text{Gy}}$ of the lungs is highly related to radiation pneumonitis, and is usually used for dose constraints and evaluation of the treatment plan [29, 32]. The results of this study indicate that the $V_{20\text{Gy}}$ of both lungs was lower in the DV-gEUD plan than in the DV plan. Thus, in the treatment planning process, it is necessary to reduce the dose to normal tissues while maintaining tumour control. This must be achieved within a reasonable planning time.

Currently, most IMRT planning is performed using DV-based constraints. The setting of the parameters requires skill and is closely related to the planners' experience. Learning this procedure often requires many iterations of a treatment plan. Effective tools can help planners quickly attain PTV coverage in complicated plans, thus effectively improving the sparing of OAR and rendering the plan more effective. The gEUD objective function is optional. Wu et al [14] proposed

Figure 3. Dose–volume histogram. (a) PTV; (b) heart; (c) total lung; (d) healthy tissue. DV plan, dose–volume–based intensity–modulated radiation treatment plan; DV–gEUD plan, dose–volume–based intensity–modulated radiotherapy plan with generalised equivalent uniform dose–based optimisation; PTV, planning target volume.

combining gEUD-based and DV-based optimisation approaches to overcome DVO limitations. In their method, gEUD optimisation is performed initially to search for a solution that meets or exceeds most of the treatment objectives. Two clinical cases were demonstrated: prostate cancer, and head and neck cancer. In their report, the gEUD plan provided better protection for OAR and the target coverage was similar. However, the homogeneity was slightly poorer than the DV-optimised plan [14, 35]. In our method, we started with a DV-generated plan then improved it by adding gEUD-based improvements to overcome the disadvantages of DVO. The goal was to reduce the number of iterations and to improve the optimum dose distribution. We demonstrated the technique in 10 BBC cases. The DV-gEUD plans gave superior dosimetric results regarding PTV coverage and OAR sparing than the DV plans, without sacrificing the homogeneity of dose distribution in the PTV. With the DV plan, if the objective function of optimisation is properly set, similar results to those of

the DV-gEUD plan can be obtained. Regarding the experience gained in the present study, after repeated revisions, the DV plan also attained a similar dose distribution to the DV-gEUD plan; however, the time required was 1.5–2 times as long. Thus, the gEUD module effectively saves time in treatment planning. In terms of quality assurance verification, the results of the DV plan and the DV-gEUD plan had similar pass rates, indicating that the DV-gEUD plan is an acceptable option.

The following limitations existed in the DV-based optimisation process: (1) in the DVH, each isodose curve might require multiple objective functions. For a complicated plan with multiple PTVs and OAR, it would be difficult to manage several added function settings for most commercial TPSs. (2) The objective functions cannot truly reflect the relationship between the biological reactions of tumours and OAR and the radiation dose. In some cases of prostate cancer and head, neck and lung tumours [14], a DV-based plan would not be the best

Table 3. The dosimetric results of PTV between DV and DV-gEUD plans

Parameter	DV plan	DV-gEUD plan	p-value
$V_{95\%}$ (%)	99.06 ± 0.44 (98.54–99.84)	98.92 ± 0.50 (98.37–99.87)	NS
CI	1.29 ± 0.10 (1.20–1.44)	1.32 ± 0.11 (1.21–1.46)	NS
HI	1.10 ± 0.03 (1.07–1.15)	1.11 ± 0.03 (1.06–1.10)	NS
TCP (%)	89.85 ± 1.16 (88.15–90.90)	89.90 ± 0.89 (88.33–90.81)	NS

CI, conformity index; DV plan, dose–volume based intensity–modulated radiotherapy; DV-gEUD plan, dose–volume with generalised equivalent uniform dose based intensity–modulated radiotherapy; HI, homogeneity index; NS, not statistically significant; PTV, planning target volume; TCP, tumour control probability; $V_{x\%}$, volume receiving $\geq x\%$ of the prescribed dose. Statistical significance ($p < 0.05$) is reported from a two-tailed exact paired *t*-test. Data are reported as mean $\pm$ 1 standard deviation computed over the cohort of 10 patients.

Table 4. Dosimetric results for heart

Parameter	DV plan	DV-gEUD plan	p-value
Mean dose (Gy)	19.3 ± 6.7	16.5 ± 5.7	0.002
V _{30 Gy} (%)	14.8 ± 13.7	10.0 ± 10.3	0.005
NTCP (%)	<0.01	<0.01	0.012
D _{50 cm³}	28.9 ± 8.4	26.5 ± 8.6	0.002
D _{25 cm³}	32.8 ± 8.9	30.3 ± 8.5	0.002
D _{10 cm³}	36.3 ± 8.8	34.0 ± 8.2	0.002
D _{5 cm³}	38.3 ± 8.4	36.1 ± 7.6	0.005
D _{2 cm³}	40.2 ± 7.9	38.0 ± 6.5	0.005
D _{1 cm³}	41.0 ± 7.6	39.4 ± 6.9	NS
D _{0.5 cm³}	41.9 ± 7.3	40.5 ± 6.5	NS
D _{0.1 cm³}	43.0 ± 6.8	41.8 ± 6.4	NS
V _{100%}	0.1 ± 0.0	0.0 ± 0.0	NS
V _{90%}	0.7 ± 0.2	0.5 ± 0.2	NS
V _{50%}	18.6 ± 8.9	19.9 ± 9.1	0.005
V _{10%}	93.7 ± 6.2	89.5 ± 9.8	NS
V _{5%}	100.0 ± 0.0	100.0 ± 0.0	NS

DV plan, dose–volume based intensity-modulated radiotherapy; DV-gEUD plan: dose–volume with generalised equivalent uniform dose based intensity-modulated radiotherapy; D_{y cc}, dose of the y cc volume; NS, not statistically significant; V_{x Gy}, percent volume receiving a ≥x Gy dose; NTCP, normal tissue complication probability; V_{z%}, volume receiving ≥z% of the prescribed dose.

Statistical significance ($p < 0.05$) is reported from a two-tailed exact paired *t*-test. Data are reported as mean ± 1 standard deviation computed over the cohort of 10 patients.

clinical plan. Stated simply, the optimiser will not attempt to search for a solution beyond what the planner requests. In the process of DV-based optimisation, if the operation is not stopped when the conditions meeting the requirements of the user are achieved, a better treatment plan (e.g. equivalent tumour coverage and a lower dose to OAR) may be obtainable.

gEUD-based optimisation cannot quickly or effectively determine the optimal solution because of the need to set constraints in the DVO by the planner. Thus, our method begins with planning using a DV module to determine a possible solution before finely tuning the DVHs with the DVO functions to achieve a better result. The purpose of this method is to utilise the DV optimisation module with gEUD to obtain a better treatment plan with a reduced number of trials. DV-based optimisation allows multiple constraints to be set in a DVH, and all points can be set as constraints. In practice, it is sufficient to set only one or two constraints.

It is noteworthy that the DV-based plan used in the present study is clinically acceptable. In a non-typical planning process, with reasonable objectives and acceptable criteria, once the objectives and criteria are met, IMRT optimisation stops and enters the next stage of dose calculation. With enough patience and effort, a better plan might be obtained through repeated DV-based optimisations, similar to that achieved with the DV-gEUD plan. The ultimate goal of the present research project was to obtain a better treatment plan in a more efficient way.

Additionally, we paid particular attention to reducing bias in the present study. Rather than using previously treated plans for reference, all plans were regenerated as new, using the same planning objectives. Bias was minimised by cross-validation with two equally

Table 5. Dosimetric results for total lung and healthy tissue

Parameter	DV plan	DV-gEUD plan	p-value
Total lung			
mean dose (Gy)	17.5 ± 3.5	15.0 ± 3.8	0.002
V _{30 Gy} (%)	15.8 ± 6.6	12.7 ± 5.7	0.002
V _{20 Gy} (%)	28.7 ± 7.9	23.6 ± 7.6	0.002
NTCP (%)	4.1 ± 5.2	1.7 ± 2.9	0.002
D _{50 cm³}	46.8 ± 4.1	45.3 ± 3.5	0.002
D _{25 cm³}	48.7 ± 3.7	46.7 ± 3.2	0.005
D _{10 cm³}	50.4 ± 3.7	50.0 ± 3.4	NS
D _{5 cm³}	51.2 ± 3.7	50.9 ± 3.4	NS
D _{2 cm³}	52.0 ± 3.6	52.0 ± 3.5	NS
D _{1 cm³}	52.4 ± 3.5	52.5 ± 3.4	NS
D _{0.5 cm³}	52.9 ± 3.5	52.9 ± 3.2	NS
D _{0.1 cm³}	53.5 ± 3.2	53.5 ± 3.0	NS
V _{100%}	1.2 ± 0.5	0.8 ± 0.4	NS
V _{90%}	4.0 ± 1.8	3.0 ± 1.3	NS
V _{50%}	20.9 ± 7.0	17.5 ± 3.1	0.002
V _{10%}	92.3 ± 6.2	82.0 ± 8.5	0.005
V _{5%}	95.8 ± 4.3	93.8 ± 4.5	NS
Healthy tissue			
mean dose (Gy)	18.6 ± 2.6	17.7 ± 3.1	NS

DV plan, dose–volume based intensity-modulated radiotherapy; DV-gEUD plan, dose–volume with generalised equivalent uniform dose based intensity-modulated radiotherapy; D_{y cc}, dose of the y cc volume; NS, not statistically significant; NTCP, normal tissue complication probability; V_{x Gy}, percent volume receiving a ≥x Gy dose; V_{z%}: volume receiving ≥z% of the prescribed dose.

Statistical significance ($p < 0.05$) is reported from a two-tailed exact paired *t*-test. Healthy tissue: the body contour excluded planning target volume. Data are reported as mean ± 1 standard deviation computed over the cohort of 10 patients.

experienced IMRT planners and with dose plans approved by an oncologist who specialises in BBC (the same oncologist who reviewed all of the plans).

Conclusions

A better result, obtained by starting with a DV-generated plan and then improving it by adding gEUD-based improvements, can reduce the number of trials and errors and also improve the optimum dose distribution. The DV-gEUD plans gave superior dosimetric results for treating BBC in terms of PTV coverage and OAR sparing than the DV plans, without sacrificing the homogeneity of dose distribution in the PTV.

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